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Electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia: study protocol for a randomized controlled trial

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Abstract

Introduction: Benign prostatic hyperplasia (BPH) is a disorder that costs high and is commonly seen among men aged over 40, usually accompanied by lower urinary tract symptoms (LUTS). Considering of the weakness of existing treatments, the method of acupuncture is proposed. We design this multicenter randomized trial to evaluate the efficacy and safety of electroacupuncture (EA) for relieving LUTS in men with BPH.

Methods and analysis: A two-arm, sham-controlled, subject- and assessor-blinded trial will be conducted in 11 hospitals in China to compare EA with sham electroacupuncture (SA) in treating moderate to severe LUTS of BPH among men aged 40 to 80. A total of 306 eligible male patients will be recruited and assigned at a 1:1 ratio to receive either EA or SA for 24 sessions in a succession of 8 weeks, with 24 weeks of follow-up. The primary outcome will be the proportions of participants with at least 30% reduction in the International Prostate Symptom Score (IPSS) total score from baseline at weeks 8 and 20. All statistical analyses will be conducted in accordance with the intention-to-treat principle, and a two-tailed *P* value less than 0.05 will be considered statistically significant.

Ethics and Dissemination: The trial has been approved by the institutional review board of Guang'anmen Hospital (2022-203-KY), as well as other recruitment centers. Each participant will receive the detailed information of the trial, and sign the written informed consent. The results of the trial are expected to be published in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov, NCT05585450. Registered on October 18, 2022.

Keywords: Electroacupuncture, Lower urinary tract symptoms, Benign prostatic hyperplasia, Clinical trial, Protocol

Strengths and limitations of this study:

1. This is the first strictly-designed multi-center, randomized, sham-controlled trial to evaluate the efficacy and safety of electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia.

2. To ensure successful blinding in this trial, needling in sham acupoints with superficial penetration and minimal electric current for 30 seconds is designed for sham acupuncture group.

3. Bias could occur as acupuncturists will be aware of the treatment allocation.

Introduction

Benign prostatic hyperplasia (BPH) is a common disorder that costs high, affecting about 36.6% of men aged over 40 years in China. [1 2] Shown in histological findings, BPH is characterized by an increase of both stromal and epithelial cells in the transitional zone of prostate that surrounds the urethra, resulting in urethra compression and resistance to urine flow, as well as obstruction-induced functional changes in bladder, such as overactivity and reduced contractility of the detrusor muscle. [3] BPH is often complicated with lower urinary tract symptoms (LUTS), including urine urgency, frequency, nocturia, dysuria, hesitancy, intermittency, and incomplete bladder emptying, which severely affect patients' quality of life (QoL), disrupting sleep patterns or interfering with daily activities. [4]

Options of the treatment to LUTS in men with BPH range from watchful waiting to medical and surgical interventions, depending on the severity of the symptoms and the level of discomfort. [5] Effective medical therapy typically involves both α-adrenergic blockers and 5α-reductase inhibitors (5-ARIs), which however may cause side effects, such as asthenia, dizziness, orthostatic hypotension (α-adrenergic blockers), [6] and reduced libido and erectile dysfunction (ED) (5-ARIs). [7] Unfortunately, it remains uncertain whether alternative medications, including plant extracts, are effective. [5] In cases where conservative therapy fails or urinary retention relapses, surgical interventions, such as transurethral resection of the prostate (TURP), may be recommended. [8 9] However, such procedures of surgery present potential risks, including retrograde ejaculation, ED, hematuria, and urinary tract infection, [10] where

approximately 5%-10% of the post-surgery patients require repeated surgery within 10 years. [11] In view of the drawbacks of the medical and surgical interventions, alternative therapies of efficacy and safety are urgently needed.

A series of studies suggested that acupuncture is an effective option of treatment to urological conditions including urinary incontinence [12] [13] and chronic prostatitis/chronic pelvic pain syndrome. [14] According to our previous studies, [15] as well as the recent researches, [16] [17] and a systematic review, [18] acupuncture may relieve LUTS and improve QoL in patients with BPH However, the effects of acupuncture remain uncertain due to small sample sizes, and lack of proper designs. Therefore, we intend to design and conduct this randomized controlled trial to evaluate the efficacy and safety of electroacupuncture (EA) in relieving LUTS in men with BPH.

Methods

Study design

This multi-center, randomized, sham-controlled, subject- and assessor-blinded trial will be performed at 11 hospitals in China, which are Guang'anmen Hospital, Acupuncture and Moxibustion Hospital of China Academy of Chinese Medical Sciences (CACMS), Affiliated Hospital of Nanjing University of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, The First Affiliated Hospital of Anhui University of Chinese Medicine, The First Affiliated Hospital of Hunan University of Chinese Medicine, West China Hospital of Sichuan University, The Second Affiliated Hospital of Guiyang University of Traditional

Chinese Medicine, Jinan Hospital of Traditional Chinese Medicine, Qingdao Hospital of Traditional Chinese Medicine, and Yantai Hospital of Traditional Chinese Medicine.

This design and protocol were developed in accordance with the guidelines for clinical trials and the standards for reporting interventions in acupuncture-based clinical trials. The study was approved by the institutional review boards at the coordinating center (ethical approval number: 2022-203-KY) and other study centers, and it has been registered at ClinicalTrials.gov on October 18, 2022 (Identifier: NCT05585450). Two parallel-arm groups, the EA group and the sham electroacupuncture (SA) group, are comprised within the framework of this trial. The study will span over a period of 33 weeks for each participant, which includes a baseline week before randomization, 8 weeks of treatment, and 24 weeks of follow-up.

Recruitment

From March 2023 to December 2025, a total of 306 male participants will be recruited through various public advertisements, such as posters, hospital websites, and WeChat public accounts. Urologists will be in charge of the screening and diagnosis, and conduct an array of evaluation, including a detailed medical history, physical examinations (mainly digital-rectal examination), urinalysis, ultrasound for the prostate, PVR, uroflowmetry, and prostate-specific antigen (PSA). The research assistants will inform all participants with a thorough explanation of the potential benefits and risks associated with this trial, the randomized allocation of treatments, and the enrollment. Each participant will sign a written informed consent before the enrollment and has the

right to withdraw from the trial at any time.

Inclusion criteria

Participants will be included if they have:

1. Diagnosis for LUTS attributed to BPH in accordance with the guidelines of European Association of Urology (EAU) [5] and American Urological Association (AUA) [19];

2. Men aged between 40 and 80 years;

3. LUTS due to BPH for at least 3 months;

4. IPSS total score ≥ 8;

5. Prostate volume ≥ 20 mL;

6. Maximum urinary flow rate (Qmax) ≤ 15 mL/s;

7. Voluntarily participate in the trial and sign the written informed content.

Exclusion criteria

Participants will be excluded if they have:

1. PVR volume ≥ 150 mL;

2. Acute urinary retention or catheterization within the 3 months;

3. Prostate cancer or PSA level ≥ 4.0 ng/mL;

4. Neurogenic lower urinary tract dysfunction; prostatitis; urinary tract infections; urethral strictures; bladder diverticula; bladder stones; bladder cancer; history of genitourinary system surgery (prostate, bladder, urethra, etc.);

5. Previous acupuncture treatment for BPH in the preceding one month, or usage of α-blockers, 5α-reductase inhibitor, muscarinic receptor antagonists, or any other specific medication in the previous two weeks unless a stable 5α-reductase inhibitor usage of over 3 months;

6. Severe lung, heart, liver, kidney, metabolic, or mental illness, coagulation dysfunction, or with obvious cognitive dysfunction;

7. Installed cardiac pacemaker, allergy to metal, severe fear of acupuncture or unbearable to the stimulation of EA.

Randomization and blinding

The allocation sequence will be generated independently by Lnkmed Tech Co. Ltd. (Beijing, China). Eligible participants will be randomly assigned in a 1:1 ratio to either the EA group or the SA group using both stratification by site and permuted blocks with random block sizes. Research assistants who are not engaged in intervention and evaluation will have access to the participant allocation information via a central randomization system. The treatment allocations will be concealed from the participants, outcome assessors, and statisticians to ensure blinding.

Intervention

EA group

The acupoint protocol is based on the meridian theory of traditional Chinese medicine, the results of previous studies, [15] and the consensus of experienced

acupuncturists from CACMS. Participants in the EA group will receive treatment at bilateral Bladder Meridian 32 (BL32, Ciliao), BL33 (Zhongliao), BL35 (Huiyang), and Spleen Meridian 6 (SP6, Sanyinjiao). BL32 and BL33 are located in the second and third posterior sacral foramen, respectively; BL35 is located 0.5 cun (≈10 mm) lateral to the extremity of the coccyx; SP6 is located posterior to the medial border of the tibia, 3 cun (≈ 60 mm) superior to the prominence of the medial malleolus.

BL32 and BL33 will be inserted by needles of 0.30×75 mm size at an angle of 50°-75°, inward and downward, to a depth of 60-70 mm. BL35 will be inserted by the same size needles, slightly outward and upward, to a depth of 60-70 mm. SP6 will be inserted vertically by needles of 0.30×40 mm to a depth of 25-30 mm. After insertion, the needles located at BL35 and SP6 will be lifted, thrust, and twisted evenly three times to induce the sensation of *deqi*. The EA therapeutic apparatus (Yingdi KWD 808I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device Co., Ltd) will be connected transversally to four pairs of needles, with a continuous wave of 5 Hertz (Hz) and an electric current ranging from 0.5-4 milliamperes (mA) for 30 minutes, depending on the participant's comfort level.

SA group

Participants in the SA group will receive superficial needling at bilateral non-acupoints lateral to the corresponding acupoints (1 cun [≈20mm] horizontally outside BL32, BL33, and BL35; sham SP6, in the middle of SP6 and tendons). The four pairs of non-acupoints will be inserted by needles of 0.30×25 mm or 0.30×40 mm size to a depth of 2-3 mm until the needles can stand still. No manipulation will be performed,

and the sensation of *deqi* will not be induced. The same EA therapeutic apparatus will be connected transversally to four pairs of needles, with a continuous wave of 5 Hz and a minimal electric current ranging from (ideally at a degree which participant can just perceive). After 30 seconds, the electric current will be turned down, leaving the indicator light, and ticking sound on.

The treatment in both groups will last 30 minutes for each session, 3 sessions per week (ideally every other day) for a succession of 8 weeks. At least two acupuncturists who had 5-year undergraduate education in acupuncture and more than 2-year clinical experience will administer treatment at each center. To guarantee the consistency in treatments, acupuncturists will receive standardized operation procedure training before conducting treatments. This training includes a video tutorial that will provide detailed information on how to perform both EA and SA correctly.

The administration of medications or other therapies for LUTS will be discouraged throughout this trial unless the symptoms become intolerable. However, the stable usage of a 5α-reductase inhibitor for over 3 months is deemed permissible. The treatment details will be recorded accordingly, including the name and the duration.

Outcomes

Primary outcome

The two co-primary outcomes include the proportions of participants with at least 30% reduction in the IPSS total score from baseline at weeks 8 and 20.

Secondary outcomes

Secondary outcomes will be measured by a range of tools, including the IPSS total score and subscales of voiding, storage, and numbers of nocturia, the IPSS QoL, the BPH Impact Index (BPH-II), and hours of undisturbed sleep (HUS) at weeks 4, 8, 12, 20, and 32; the International Index of Erectile Function 5 (IIEF-5), the Hospital Anxiety and Depression Scale (HADS), and the Patient Global Index of Improvement (PGI-I) at weeks 8, 20, and 32. The volume of the prostate and post-void residual urine, maximum and average flow-rate will also be measured at week 8 (Figure 2). The secondary outcome measures and the time frame are shown in Table 1.

The IPSS is a 7-item, reliable, valid, and sensitive questionnaire that is commonly used to assess the severity of LUTS, including filling (urgency, frequency, and nocturia) and voiding (incomplete emptying, intermittency, straining, and weak urinary stream) symptoms. [20-22] The score of IPSS ranges from 0 to 35, with scores of 0 to 7 indicating mild symptoms; 8 to 19 indicating moderate symptoms; and 20 to 35 indicating severe symptoms. [22] It has been established that a decrease of at least 3 points is the minimal clinically important difference (MCID), [23] while a 30% reduction in the IPSS total score is the minimal clinical improvement recommended by the U.S. Food and Drug Administration (FDA) for device therapy. [24]

The IPSS QoL includes only one specific question: if you are to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? The response is categorized into 7 levels, with a score ranging from 0 to 6, and higher scores indicating poorer QoL. Despite its simplicity, this question is strongly associated with the overall symptom score. [25]

The BPH-II is a 4-item, self-administered tool that measures the interference of LUTS in participants' physical, mental, and usual activities over the past month. The score of BPH-II ranges from 0 to 13, with higher scores indicating greater BPH symptom-related impact. [26]

The IIEF-5 is an abridged, 5-item instrument for evaluating erection dysfunction, ranging from 1 to 25 (normal, 22-25; mild, 17-21; mild to moderate, 12-16; moderate, 8-11, or severe, 1-7). [27 28]

The HUS is defined as the duration from falling asleep till awake in the morning, or till the first nocturia if any. [29]

The HADS is developed to quantify psychological distress, consisting of two 7-item subscales, one for anxiety and one for depression. The total score ranges from 0 to 42, with higher scores indicating worse conditions. [30]

The PGI-I evaluates the overall treatment effect as perceived by the participants themselves. The change can be rated in 7 levels, including "very much better", "much better", "a little better", "no change", "a little worse", "much worse" or "very much worse". [31]

Table 1 Secondary outcome measures

No.	Outcome measure	Time frame
1	Proportions of participants with at least 30% reduction in the International Prostate Symptom Score (IPSS) total score from baseline	Weeks 4, 12, and 32 [a]
2	Proportions of participants with at least 50% reduction in the IPSS total score from baseline	Weeks 4, 8, 12, 20, and 32
3	Changes in the IPSS total score from baseline	Weeks 4, 8, 12, 20, and

		32
4	Changes in the IPSS subscale scores, including filling and voiding, from baseline	Weeks 4, 8, 12, 20, and 32
5	Changes in the number of nocturia from baseline	Weeks 4, 8, 12, 20, and 32
6	Changes in the IPSS quality of life (QoL) item from baseline	Weeks 4, 8, 12, 20, and 32
7	Changes in the Benign Prostatic Hyperplasia Impact Index (BPH-II) from baseline	Weeks 4, 8, 12, 20, and 32
8	Changes in the International Index of Erectile Function 5 (IIEF-5) from baseline	Weeks 8, 20, and 32
9	Changes in the hours of undisturbed sleep (HUS) from baseline	Weeks 4, 8, 12, 20, and 32
10	Changes from baseline in the Hospital Anxiety and Depression Scale (HADS) from baseline	Weeks 8, 20, and 32
11	Changes in the volume of the prostate from baseline	Week 8
12	Changes in the volume of the post-void residual urine	Week 8
13	Changes in the maximum and average flow-rate from baseline	Week 8
14	Proportions of responders per the Patient Global Index of Improvement (PGI-I)	Weeks 8, 20, and 32

[a] The key secondary outcome is the proportion of participants with at least 30% reduction in the IPSS total score from baseline at week 32.

Expectation and brief assessment

To assess participants' expectations of improvement in LUTS, participants will be asked: how do you expect the LUTS to be in 8 weeks at baseline. To assess participants' belief of EA, at both baseline and week 8, participants will be asked: do you think that EA may be beneficial in treating your BPH?

Blinding assessment

Participants will be informed that there is a 50% chance of being allocated to receive either the traditional EA with deeper needling or the SA with shallower needling. After the last session at week 8, each participant will be asked whether they have received traditional EA, with the option of "Yes" or "No".

Safety assessment

EA-associated adverse events, such as bruising, hematomas, infection, or numbness as well as any other adverse events unrelated to EA, will be carefully documented. Serious adverse events will be reported to the institutional review boards of Guang'anmen Hospital within 24 hours.

Data management and quality control

To ensure the consistency, personnel in each recruitment center will receive extensive training from the principal investigator (Z. Liu) on details of the protocol.

All treatments for each participant will be completed by 1-2 specific acupuncturists. In addition, one assessor must maintain responsibility for the same participants throughout the trial. They will explain the contents of handbook, if necessary, as well as remind the participants of their schedule through either phone or WeChat. At each assessment visit, the data will be collected and recorded in the paper case report form (CRF) promptly by assessors. The clinical research coordinators will type the data into the electronic data capture (EDC) system within 1 week. The clinical research associates (CRA) will supervise weekly through the system to enhance the

quality. All data on the EDC system will be locked upon verification of consistency between data online and the paper CRFs by two independent CRAs.

All deviations from the study protocol will be reported in time. Participants who withdraw or drop out will be documented during the trial. Lnkmed Tech Co. Ltd. (Beijing, China) will be responsible to conceal the treatment allocation, which will only be revealed after the statistical analysis is completed.

Statistical methods

Sample size

To estimate the sample size, we will assume the proportions of participants with at least 30% reduction in the IPSS total score from baseline at week 8 to be 75% in the EA group and 55% in the SA group based on the results of our unpublished study, which showed that the primary outcome at week 8 was 77% among the group receiving EA and 55% among the SA group. The study needed 236 participants to achieve 90% power with a 2-sided α level of 0.05. Assuming a 20% dropout or withdrawal rate, the study will need 306 participants to provide 90% power with a 2-sided α level of 0.05.

Statistical analysis

The two null hypotheses are that EA will be the equal to SA at both weeks 8 and 20, and as well as week 32. The primary outcome will be analyzed using a generalized linear model with a binomial distribution and identity link. Changes from baseline in the IPSS total score will be analyzed using a mixed-effects models for repeated measures. The observed change from baseline at each visit will be considered as the

dependent variable. The same approach will be used in other longitudinal continuous outcomes, such as IPSS subscales (filling, voiding, and nocturia), BPH-II scores. The PGI-I, participants' expectations and brief assessment, adherence, blinding and adverse event data will be provided for descriptive purposes only.

Multiplicity on the primary outcome will be controlled by a closed testing procedure. [32] In the closed testing procedure for the primary outcome, EA and SA will only be compared at week 32 when the comparisons between EA and SA have to be positive (p-value lower than 0.05) at weeks 8 and 20. Secondary analyses will be considered supportive in nature and will be not controlled for multiplicity. The sensitivity analysis of the primary outcome will be repeated using 2 analytical approaches. First, multiple imputation will be used to impute missing IPSS total score. Second, the baseline usage of the 5α-reductase inhibitor will be used as a covariate in the primary analysis.

All analyses will be conducted using SAS version 9.4 (SAS Institute) in accordance with the intention-to-treat principle, and a two-tailed *P* value less than 0.05 will be considered statistically significant.

Ethics and dissemination

The trial has been approved by the institutional review board of Guang'anmen Hospital (2022-203-KY), as well as other recruitment centers, and will be conducted in accordance with the Declaration of Helsinki. Each participant will receive the detailed information of the trial, and sign the written informed consent. Those in the SA group

will be compensated with 24-session EA treatment. The results of the trial are expected to be published in a peer-reviewed journal.

Discussion

Patients with BPH can be managed with watchful waiting when no complications set in and IPSS ≤ 7, although histological evidence and enlarged prostates may exist. [4] However, patients with moderate to severe BPH may suffer in daily activities and face huge financial burden. [4 33] In addition, low Qmax may indicate detrusor underactivity ,[34] and Qmax less than 15 mL/s may indicate bladder outlet obstruction (BOO), which sensitivity was tested 82% [35] and poorly relieved by ablative technique, a minimal invasive treatment. [5] Whereas, EA could alleviate LUTS by augmenting detrusor contractions and diminishing obstructions. [36] Therefore, this study will focus on patients with LUTS more than 3 months, IPSS score over 8 points, and Qmax ≤ 15 mL/s.

Medical therapy, such as 5-ARIs, could reduce prostate volume and slow down the progression of the disease, with gradual effects, taking as long as 3 to 6 months to respond. As the long-term of usage of the medication might lead to unacceptable side effects, like ED, [37] many patients in China turned to acupuncture treatment, a complementary and alternative therapy that is effective and safe in public view. This study will adopt standardized acupuncture scheme based on the meridian theory and clinical experiences. Stimulation at acupoint of SP 6, which is located over the posterior tibial nerve and is the crossroad of intersection of the Spleen, Kidney, and Liver

Meridians, has been found beneficial in relieving LUTS. [38 39] Similarly, the acupoints along Bladder Meridian, such as BL32 and BL33, have been regularly used to address urologic disorders, for the points are located in the sacral hiatus where nerves of loin and sacrum traverse and the stimulation could benefit LUTS. [40 41] However, it's challenging to set up an ideal sham control in acupuncture clinical trials. To ensure successful blinding in this trial, needling in sham acupoints with superficial penetration and minimal electric current for 30 seconds is designed for SA group where therapeutic effects may present nevertheless. [42]

The hypothesis of this trial is that EA is superior to SA in relieving LUTS in patients with moderate-to-severe BPH. The efficacy will be mainly reflected in the proportions of patients whose IPSS total score is reduced by 30% or more from baseline, a level of the minimal clinical improvement recommended by the U.S. FDA for device therapy. [24] Based on our clinical experience and unpublished pilot study, this trial will select weeks 8 and 20 as the primary outcome timepoints to evaluate the immediate effects after 8-week treatment and the sustained effects after 12-week cessation of treatment. Furthermore, to provide deeper insights into its clinical significance, an extended long-term follow-up will be conducted at week 32, which serves as the key secondary outcome timepoint.

Although the study will intend to provide robust evidence on efficacy and safety of EA in treating BPH by blinding outcome assessors and patients, bias could occur as acupuncturists will be aware of the treatment allocation. In addition, the results of this trial may not be generalized globally as the trial will be performed in China only.

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Contributions

Zhu Lili, Yan Yan, Liu Zhishun: Conceived and designed the experiments; Wrote the paper. Yu Jinna, Sun Yuanjie, Chen Yu, Fang Jiufei: Performed the experiments; Wrote the paper. Liu Yan: Analyzed and interpreted the data; Wrote the paper. All authors have read and approved to the final version.

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Competing interest

The authors declare no competing interests.

Figure 1. Study flowchart

Abbreviations: BPH, Benign Prostatic Hyperplasia

Figure 2. Study Schedule

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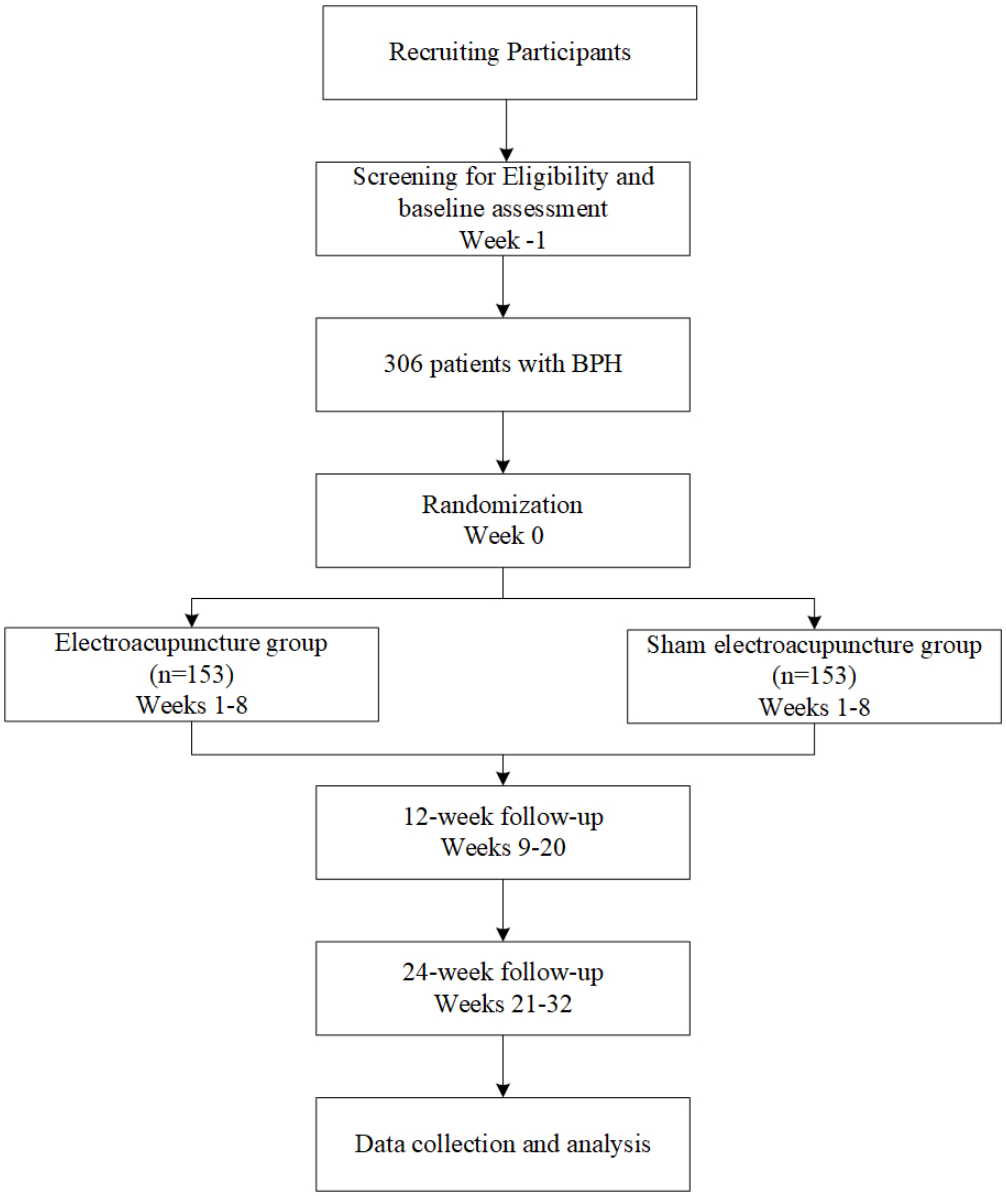

Figure 1. Study flowchart

405x480mm (57 x 57 DPI)

Figure 2. Study Schedule

	STUDY PERIOD											
	Enrolment	Allocation	Post-allocation									
			Treatment								Follow-up	
TIMEPOINTS(week)	*-1*	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*12*	*20*	*32*
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Demographics	X												
Medical history	X												
Allocation		X											
INTERVENTIONS:													
Electroacupuncture			◆	—	—	—	—	—	—	◆			
Sham electroacupuncture			◆	—	—	—	—	—	—	◆			
ASSESSMENTS:													
IPSS	X					X				X	X	X	X
QoL	X					X				X	X	X	X
BPH-II	X					X				X	X	X	X
IIEF-5	X									X		X	X
HADS	X									X		X	X
HUS	X					X				X	X	X	X
Volume of prostate	X									X			
PVR	X									X			
Urinary flow-rate	X									X			
PSA	X												
PGI-I										X		X	X
Expectation assessment	X												
Brief assessment	X									X			
Blinding assessment										X			
Safety assessment	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BPH-II, Benign Prostatic Hyperplasia Impact Index; HADS, Hospital Anxiety and Depression Scale; HUS, Hours of Undisturbed Sleep; IIEF-5, International Index of Erectile Function 5; IPSS, International Prostate Symptom Score; QoL, Quality of Life; PGI-I, Patient Global Index of Improvement; PSA, Prostate-specific Antigen; PVR, Post-void Residual.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: Page 2-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry: Page 2
	2b	All items from the World Health Organization Trial Registration Data Set: NA
Protocol version	3	Date and version identifier: NA
Funding	4	Sources and types of financial, material, and other support: Page 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors: Page 1,19
	5b	Name and contact information for the trial sponsor: NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee): Page 14-15
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: Page 4-5
	6b	Explanation for choice of comparators: Page 4-5
Objectives	7	Specific objectives or hypotheses: Page 5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory): Page 5-6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained: Page 5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists): Page 7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: Page 8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease): NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests): NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial: Page 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended: Page 10-14, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure): Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations: Page 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size: Page 6-7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions: Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned: Page 8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions: Page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how: Page 8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial: NA
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol: Page 14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: Page 14-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol: Page 14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol: Page 15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses): Page 15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation): Page 15-16

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed: NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial: NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct: Page 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor: NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: Page 16-17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators): NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32): Page 16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable:NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial: Page 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site: Page 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators: NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation: NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions: NA
	31b	Authorship eligibility guidelines and any intended use of professional writers: NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code: NA
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates: NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable: NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia: study protocol for a randomized controlled trial

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
Keywords:	Clinical Trial, Prostate disease < UROLOGY, Prostate

Electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia: study protocol for a randomized controlled trial

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Abstract

Introduction: Benign prostatic hyperplasia (BPH) is a condition commonly seen among men aged over 40, significantly affecting their quality of life and typically accompanied by lower urinary tract symptoms (LUTS). Acupuncture presents a potentially effective treatment option; however, the exact effects remain uncertain. Therefore, we design this multicenter randomized trial to evaluate the efficacy and safety of electroacupuncture (EA) for relieving LUTS in men with BPH.

Methods and analysis: A two-arm, sham-controlled, subject- and assessor-blinded trial will be conducted in 11 hospitals in China to compare EA with sham electroacupuncture (SA) in treating moderate to severe LUTS of BPH among men aged 40 to 80. A total of 306 eligible male patients will be recruited and assigned at a 1:1 ratio to receive either EA or SA for 24 sessions over a succession of 8 weeks, with 24 weeks of follow-up. The primary outcome will be the proportions of participants with at least 30% reduction in the International Prostate Symptom Score total score from baseline at weeks 8 and 20. All statistical analyses will be conducted in accordance with the intention-to-treat principle, and a two-tailed *P* value less than 0.05 will be considered statistically significant.

Ethics and Dissemination: The trial has been approved by the institutional review board of Guang'anmen Hospital (2022-203-KY), as well as other recruitment centers. Each participant will receive the detailed information of the trial, and sign the written informed consent. The results of the trial are expected to be published in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov, NCT05585450. Registered on October 18, 2022.

Keywords: Electroacupuncture, Lower urinary tract symptoms, Benign prostatic hyperplasia, Clinical trial, Protocol

Strengths and limitations of this study:

1. This is the first strictly-designed multi-center, randomized, sham-controlled trial to evaluate the efficacy and safety of electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia.
2. To ensure successful blinding in this trial, needling in sham acupoints with superficial penetration and minimal electric current for 30 seconds is designed for sham acupuncture group.
3. Bias may occur as acupuncturists will be aware of the treatment allocation

Introduction

Benign prostatic hyperplasia (BPH) is a common disorder that affecting about 36.6% of men aged over 40 years in China. [1 2] Shown in histological findings, BPH is characterized by an increase of both stromal and epithelial cells in the transitional zone of prostate, which surrounds the urethra. This leads to urethra compression and resistance to urine flow, as well as obstruction-induced functional changes in bladder, termed benign prostatic obstruction (BPO), such as overactivity and reduced contractility of the detrusor muscle. [3] According to the European Association of Urology (EAU) guideline, there is a growing tendency to avoid using the term BPH to describe lower urinary tract symptoms (LUTS) that are actually a consequence of BPO. [4] LUTS encompass a spectrum of symptoms including urine urgency, frequency, nocturia, dysuria, hesitancy, intermittency, and incomplete bladder emptying, which severely affect patients' quality of life (QoL), disrupting sleep patterns or interfering with daily activities. [5]

Options of the treatment to LUTS in men with BPH range from watchful waiting to medical and surgical interventions, depending on the severity of the symptoms and the level of discomfort. [4] Effective medical therapy typically involves both α-adrenergic blockers and 5α-reductase inhibitors (5-ARIs); however, these medications may cause side effects, such as asthenia, dizziness, orthostatic hypotension (α-adrenergic blockers), [6] and reduced libido and erectile dysfunction (ED) (5-ARIs). [7] Unfortunately, it remains uncertain whether alternative medications, including plant extracts, are effective. [4] In cases where conservative therapy fails or urinary retention relapses, surgical

interventions, such as transurethral resection of the prostate (TURP), may be recommended. [8 9] However, such procedures of surgery present potential risks, including retrograde ejaculation, ED, hematuria, and urinary tract infection, [10] where approximately 5%-10% of the post-surgery patients require repeated surgery within 10 years. [11] In view of the drawbacks of the medical and surgical interventions, alternative therapies of efficacy and safety are urgently needed.

A series of studies have suggested that acupuncture is an effective treatment option for urological conditions, including urinary incontinence [12 13] and chronic prostatitis/chronic pelvic pain syndrome. [14] According to our previous studies, [15] as well as the recent researches, [16 17] and a systematic review, [18] acupuncture may relieve LUTS and improve QoL in patients with BPH. However, the effects of acupuncture remain uncertain due to small sample sizes, and lack of proper designs. Therefore, we intend to design and conduct this randomized controlled trial to evaluate the efficacy and safety of electroacupuncture (EA) in relieving LUTS in men with BPH.

Methods

Study design

This multi-center, randomized, sham-controlled, subject- and assessor-blinded trial will be performed at 11 hospitals in China, which are Guang'anmen Hospital, Acupuncture and Moxibustion Hospital of China Academy of Chinese Medical Sciences (CACMS), Affiliated Hospital of Nanjing University of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, The First

Affiliated Hospital of Anhui University of Chinese Medicine, The First Affiliated Hospital of Hunan University of Chinese Medicine, West China Hospital of Sichuan University, The Second Affiliated Hospital of Guiyang University of Traditional Chinese Medicine, Jinan Hospital of Traditional Chinese Medicine, Qingdao Hospital of Traditional Chinese Medicine, and Yantai Hospital of Traditional Chinese Medicine.

This design and protocol were developed in accordance with the guidelines for clinical trials and the standards for reporting interventions in acupuncture-based clinical trials. The study was approved by the institutional review boards at the coordinating center (ethical approval number: 2022-203-KY) and other study centers, and it has been registered at ClinicalTrials.gov on October 18, 2022 (Identifier: NCT05585450). Two parallel-arm groups, the EA group and the sham electroacupuncture (SA) group, are comprised within the framework of this trial. The study will span over a period of 33 weeks for each participant, which includes a baseline week before randomization, 8 weeks of treatment, and 24 weeks of follow-up (Figure 1).

Recruitment

The planned start date was 20 October 2022; however, due to the COVID-19 pandemic, actual enrollment began on 9 March 2023. The estimated end date is 30 December 2025. A total of 306 male participants will be recruited through various public advertisements, such as posters, hospital websites, and WeChat public accounts. Urologists will be in charge of the screening and diagnosis, and conduct an array of evaluation, including a detailed medical history, physical examinations (mainly digital-

rectal examination), urinalysis, ultrasound for the prostate, post-void residual urine (PVR), uroflowmetry, and prostate-specific antigen (PSA). The research assistants will inform all participants with a thorough explanation of the potential benefits and risks associated with this trial, the randomized allocation of treatments, and the enrollment. Each participant will sign a written informed consent before the enrollment and has the right to withdraw from the trial at any time.

Inclusion criteria

Participants will be included if they have:

1. Diagnosis for LUTS attributed to BPH in accordance with the guidelines of EAU [4] and American Urological Association (AUA) [19];

2. Men aged between 40 and 80 years;

3. LUTS due to BPH for at least 3 months;

4. International Prostate Symptom Score (IPSS) total score ≥ 8;

5. Prostate volume ≥ 20 mL;

6. Maximum urinary flow rate (Qmax) ≤ 15 mL/s;

7. Voluntarily participate in the trial and sign the written informed content.

Exclusion criteria

Participants will be excluded if they have:

1. PVR volume ≥ 150 mL;

2. Acute urinary retention or catheterization within the 3 months;

3. Prostate cancer or PSA level ≥ 4.0 ng/mL;

4. Neurogenic lower urinary tract dysfunction; prostatitis; urinary tract infections; urethral strictures; bladder diverticula; bladder stones; bladder cancer; history of genitourinary system surgery (prostate, bladder, urethra, etc.);

5. Previous acupuncture treatment for BPH in the preceding one month, or usage of α-blockers, 5α-reductase inhibitor, muscarinic receptor antagonists, or any other specific medication in the previous two weeks unless a stable 5α-reductase inhibitor usage of over 3 months;

6. Severe lung, heart, liver, kidney, metabolic, or mental illness, coagulation dysfunction, or with obvious cognitive dysfunction;

7. Installed cardiac pacemaker, allergy to metal, severe fear of acupuncture or unbearable to the stimulation of EA.

Randomization and blinding

The allocation sequence will be generated independently by Lnkmed Tech Co. Ltd. (Beijing, China). Eligible participants will be randomly assigned in a 1:1 ratio to either the EA group or the SA group using both stratification by site and permuted blocks with random block sizes. Research assistants who are not engaged in intervention and evaluation will have access to the participant allocation information via a central randomization system. The treatment allocations will be concealed from the participants, outcome assessors, and statisticians to ensure blinding.

Intervention

EA group

The acupoint protocol is based on the meridian theory of traditional Chinese medicine, the results of previous studies, [15] and the consensus of experienced acupuncturists from CACMS. Participants in the EA group will receive treatment at bilateral Bladder Meridian 32 (BL32, Ciliao), BL33 (Zhongliao), BL35 (Huiyang), and Spleen Meridian 6 (SP6, Sanyinjiao). BL32 and BL33 are located in the second and third posterior sacral foramen, respectively; BL35 is located 0.5 cun (≈10 mm) lateral to the extremity of the coccyx; SP6 is located posterior to the medial border of the tibia, 3 cun (≈ 60 mm) superior to the prominence of the medial malleolus.

BL32 and BL33 will be inserted by needles of 0.30×75 mm size at an angle of 50°-75°, inward and downward, to a depth of 60-70 mm. BL35 will be inserted by the same size needles, slightly outward and upward, to a depth of 60-70 mm. SP6 will be inserted vertically by needles of 0.30×40 mm to a depth of 25-30 mm. After insertion, the needles located at BL35 and SP6 will be lifted, thrust, and twisted evenly three times to induce the sensation of *deqi*. The EA therapeutic apparatus (Yingdi KWD 808I electro pulse acupuncture therapeutic apparatus, Changzhou Yingdi Electronic Medical Device Co., Ltd) will be connected transversally to four pairs of needles, with a continuous wave of 5 Hertz (Hz) and an electric current ranging from 0.5-4 milliamperes (mA) for 30 minutes, depending on the participant's comfort level.

SA group

Participants in the SA group will receive superficial needling at bilateral non-

acupoints lateral to the corresponding acupoints (1 cun [≈20mm] horizontally outside BL32, BL33, and BL35; sham SP6, in the middle of SP6 and tendons). The four pairs of non-acupoints will be inserted by needles of 0.30×25 mm or 0.30×40 mm size to a depth of 2-3 mm until the needles can stand still. No manipulation will be performed, and the sensation of *deqi* will not be induced. The same EA therapeutic apparatus will be connected transversally to four pairs of needles, with a continuous wave of 5 Hz and a minimal electric current ranging from (ideally at a degree which participant can just perceive). After 30 seconds, the electric current will be turned down, leaving the indicator light, and ticking sound on.

The treatment in both groups will last 30 minutes for each session, 3 sessions per week (ideally every other day) for a succession of 8 weeks. At least two acupuncturists who had 5-year undergraduate education in acupuncture and more than 2-year clinical experience will administer treatment at each center. To guarantee the consistency in treatments, acupuncturists will receive standardized operation procedure training before conducting treatments. This training includes a video tutorial that will provide detailed information on how to perform both EA and SA correctly.

The administration of medications or other therapies for LUTS will be discouraged throughout this trial unless the symptoms become intolerable. However, the stable usage of a 5α-reductase inhibitor for over 3 months is deemed permissible. The treatment details will be recorded accordingly, including the name and the duration.

Outcomes

Primary outcome

The two co-primary outcomes include the proportions of participants with at least 30% reduction in the IPSS total score from baseline at weeks 8 and 20.

Secondary outcomes

Secondary outcomes will be measured by a range of tools, including the IPSS total score and subscales of voiding, storage, and numbers of nocturia, the IPSS QoL, the BPH Impact Index (BPH-II), and hours of undisturbed sleep (HUS) at weeks 4, 8, 12, 20, and 32; the International Index of Erectile Function 5 (IIEF-5), the Hospital Anxiety and Depression Scale (HADS), and the Patient Global Index of Improvement (PGI-I) at weeks 8, 20, and 32. The volume of the prostate and post-void residual urine, maximum and average flow-rate will also be measured at week 8 (Figure 2). The secondary outcome measures and the time frame are shown in Table 1.

The IPSS is a 7-item, reliable, valid, and sensitive questionnaire that is commonly used to assess the severity of LUTS, including filling (urgency, frequency, and nocturia) and voiding (incomplete emptying, intermittency, straining, and weak urinary stream) symptoms. [20-22] The score of IPSS ranges from 0 to 35, with scores of 0 to 7 indicating mild symptoms; 8 to 19 indicating moderate symptoms; and 20 to 35 indicating severe symptoms. [22] It has been established that a decrease of at least 3 points is the minimal clinically important difference (MCID), [23] while a 30% reduction in the IPSS total score is the minimal clinical improvement recommended by the U.S. Food and Drug Administration (FDA) for device therapy. [24]

The IPSS QoL includes only one specific question: if you are to spend the rest of

your life with your urinary condition just the way it is now, how would you feel about that? The response is categorized into 7 levels, with a score ranging from 0 to 6, and higher scores indicating poorer QoL. Despite its simplicity, this question is strongly associated with the overall symptom score. [25]

The BPH-II is a 4-item, self-administered tool that measures the interference of LUTS in participants' physical, mental, and usual activities over the past month. The score of BPH-II ranges from 0 to 13, with higher scores indicating greater BPH symptom-related impact. [26]

The IIEF-5 is an abridged, 5-item instrument for evaluating erection dysfunction, ranging from 1 to 25 (normal, 22-25; mild, 17-21; mild to moderate, 12-16; moderate, 8-11, or severe, 1-7). [27 28]

The HUS is defined as the duration from falling asleep till awake in the morning, or till the first nocturia if any. [29]

The HADS is developed to quantify psychological distress, consisting of two 7-item subscales, one for anxiety and one for depression. The total score ranges from 0 to 42, with higher scores indicating worse conditions. [30]

The PGI-I evaluates the overall treatment effect as perceived by the participants themselves. The change can be rated in 7 levels, including "very much better", "much better", "a little better", "no change", "a little worse", "much worse" or "very much worse". [31]

Table 1 Secondary outcome measures

No.	Outcome measure	Time frame

1	Proportions of participants with at least 30% reduction in the International Prostate Symptom Score (IPSS) total score from baseline	Weeks 4, 12, and 32 [a]
2	Proportions of participants with at least 50% reduction in the IPSS total score from baseline	Weeks 4, 8, 12, 20, and 32
3	Changes in the IPSS total score from baseline	Weeks 4, 8, 12, 20, and 32
4	Changes in the IPSS subscale scores, including filling and voiding, from baseline	Weeks 4, 8, 12, 20, and 32
5	Changes in the number of nocturia from baseline	Weeks 4, 8, 12, 20, and 32
6	Changes in the IPSS quality of life (QoL) item from baseline	Weeks 4, 8, 12, 20, and 32
7	Changes in the Benign Prostatic Hyperplasia Impact Index (BPH-II) from baseline	Weeks 4, 8, 12, 20, and 32
8	Changes in the International Index of Erectile Function 5 (IIEF-5) from baseline	Weeks 8, 20, and 32
9	Changes in the hours of undisturbed sleep (HUS) from baseline	Weeks 4, 8, 12, 20, and 32
10	Changes from baseline in the Hospital Anxiety and Depression Scale (HADS) from baseline	Weeks 8, 20, and 32
11	Changes in the volume of the prostate from baseline	Week 8
12	Changes in the volume of the post-void residual urine	Week 8
13	Changes in the maximum and average flow-rate from baseline	Week 8
14	Proportions of responders per the Patient Global Index of Improvement (PGI-I)	Weeks 8, 20, and 32

[a] The key secondary outcome is the proportion of participants with at least 30% reduction in the IPSS total score from baseline at week 32.

Expectation and brief assessment

To assess participants' expectations of improvement in LUTS, participants will be asked: how do you expect the LUTS to be in 8 weeks at baseline. To assess participants' belief of EA, at both baseline and week 8, participants will be asked: do you think that EA may be beneficial in treating your BPH?

Blinding assessment

Participants will be informed that there is a 50% chance of being allocated to receive either the traditional EA with deeper needling or the SA with shallower needling. After the last session at week 8, each participant will be asked whether they have received traditional EA, with the option of "Yes" or "No".

Safety assessment

EA-associated adverse events, such as bruising, hematomas, infection, or numbness as well as any other adverse events unrelated to EA, will be carefully documented. Serious adverse events will be reported to the institutional review boards of Guang'anmen Hospital within 24 hours.

Data management and quality control

To ensure the consistency, personnel in each recruitment center will receive extensive training from the principal investigator (Z. Liu) on details of the protocol.

All treatments for each participant will be completed by 1-2 specific acupuncturists. In addition, one assessor must maintain responsibility for the same participants throughout the trial. They will explain the contents of handbook, if

necessary, as well as remind the participants of their schedule through either phone or WeChat. At each assessment visit, the data will be collected and recorded in the paper case report form (CRF) promptly by assessors. The clinical research coordinators will type the data into the electronic data capture (EDC) system within 1 week. The clinical research associates (CRA) will supervise weekly through the system to enhance the quality. All data on the EDC system will be locked upon verification of consistency between data online and the paper CRFs by two independent CRAs.

All deviations from the study protocol will be reported in time. Participants who withdraw or drop out will be documented during the trial. Lnkmed Tech Co. Ltd. (Beijing, China) will be responsible to conceal the treatment allocation, which will only be revealed after the statistical analysis is completed.

Statistical methods

Sample size

To estimate the sample size, we will assume the proportions of participants with at least 30% reduction in the IPSS total score from baseline at week 8 to be 75% in the EA group and 55% in the SA group based on the results of our unpublished study, which showed that the primary outcome at week 8 was 77% among the group receiving EA and 55% among the SA group. The study needed 236 participants to achieve 90% power with a 2-sided α level of 0.05. Assuming a 20% dropout or withdrawal rate, the study will need 306 participants to provide 90% power with a 2-sided α level of 0.05.

Statistical analysis

The two null hypotheses are that EA will be the equal to SA at both weeks 8 and 20, and as well as week 32. The primary outcome will be analyzed using a generalized linear model with a binomial distribution and identity link. Changes from baseline in the IPSS total score will be analyzed using a mixed-effects models for repeated measures. The observed change from baseline at each visit will be considered as the dependent variable. The same approach will be used in other longitudinal continuous outcomes, such as IPSS subscales (filling, voiding, and nocturia), BPH-II scores. The PGI-I, participants' expectations and brief assessment, adherence, blinding and adverse event data will be provided for descriptive purposes only.

Multiplicity on the primary outcome will be controlled by a closed testing procedure. [32] In the closed testing procedure for the primary outcome, EA and SA will only be compared at week 32 when the comparisons between EA and SA have to be positive (p-value lower than 0.05) at weeks 8 and 20. Secondary analyses will be considered supportive in nature and will be not controlled for multiplicity. The sensitivity analysis of the primary outcome will be repeated using 2 analytical approaches. First, multiple imputation will be used to impute missing IPSS total score. Second, the baseline usage of the 5α-reductase inhibitor will be used as a covariate in the primary analysis.

All analyses will be conducted using SAS version 9.4 (SAS Institute) in accordance with the intention-to-treat principle, and a two-tailed *P* value less than 0.05 will be considered statistically significant.

Patient and public involvement

During the conception period of the study, we conducted interviews with a subset of BPH patients with LUTS. This allowed us to gather insights into the impact of primary symptoms on QoL, changes observed after EA, as well as the acceptance and perspectives on EA. These insights played a crucial role in later study design, particularly in determining the target population and selecting outcome measures. Patients and/or the public were not involved in the recruitment and conduct of this study. Patients who actively contributed to the consultation process for the trial design will be excluded. The results of the study will be communicated in plain language and disseminated to the public, including participants, through various public and social media channels. Participants will receive the study intervention free of charge during the study period.

Ethics and dissemination

The trial has been approved by the institutional review board of Guang'anmen Hospital (2022-203-KY), as well as other recruitment centers, and will be conducted in accordance with the Declaration of Helsinki. Each participant will receive the detailed information of the trial, and sign the written informed consent (Supplemental Material). Those in the SA group will be compensated with 24-session EA treatment. The results of the trial are expected to be published in a peer-reviewed journal.

Discussion

Patients with BPH can be managed with watchful waiting when no complications set in and IPSS ≤ 7, although histological evidence and enlarged prostates may exist. [4] However, patients with moderate to severe BPH may suffer in daily activities and face huge financial burden. [5 33] In addition, low Qmax may indicate detrusor underactivity,[34] and Qmax less than 15 mL/s may indicate bladder outlet obstruction (BOO), which sensitivity was tested 82% [35] and poorly relieved by ablative technique, a minimal invasive treatment. [4] Whereas, EA could alleviate LUTS by augmenting detrusor contractions and diminishing obstructions. [36] Therefore, this study will focus on patients with LUTS lasting more than 3 months, IPSS score over 8 points, and Qmax ≤ 15 mL/s.

Medical therapy, such as 5-ARIs, could reduce prostate volume and slow down the progression of the disease, with gradual effects, taking as long as 3 to 6 months to respond. As the long-term of usage of the medication might lead to unacceptable side effects, like ED, [37] many patients in China turned to acupuncture treatment, a complementary and alternative therapy that is effective and safe in public view. This study will adopt standardized acupuncture scheme based on the meridian theory and clinical experiences. Stimulation at acupoint of SP 6, which is located over the posterior tibial nerve and is the crossroad of intersection of the Spleen, Kidney, and Liver Meridians, has been found beneficial in relieving LUTS. [38 39] Similarly, the acupoints along Bladder Meridian, such as BL32 and BL33, have been regularly used to address urologic disorders, for the points are located in the sacral hiatus where nerves of loin and sacrum traverse and the stimulation could benefit LUTS. [40 41] However, it's

challenging to set up an ideal sham control in acupuncture clinical trials. To ensure successful blinding in this trial, needling in sham acupoints with superficial penetration and minimal electric current for 30 seconds is designed for SA group where therapeutic effects may present nevertheless. [42]

The hypothesis of this trial is that EA is superior to SA in relieving LUTS in patients with moderate-to-severe BPH. The efficacy will be mainly reflected in the proportions of patients whose IPSS total score is reduced by 30% or more from baseline, a level of the minimal clinical improvement recommended by the U.S. FDA for device therapy. [24] Based on our clinical experience and unpublished pilot study, this trial will select weeks 8 and 20 as the primary outcome timepoints to evaluate the immediate effects after 8-week treatment and the sustained effects after 12-week cessation of treatment. Furthermore, to provide deeper insights into its clinical significance, an extended long-term follow-up will be conducted at week 32, which serves as the key secondary outcome timepoint.

Although the study will intend to provide robust evidence on efficacy and safety of EA in treating BPH by blinding outcome assessors and patients, bias could occur as acupuncturists will be aware of the treatment allocation. In addition, the results of this trial may not be generalized globally as the trial will be performed in China only.

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Contributions

Lili Zhu, Yan Yan, Zhishun Liu: Conceived and designed the experiments; Wrote the paper. Jinna Yu, Yuanjie Sun, Yu Chen, Jiufei Fang: Performed the experiments; Wrote the paper. Yan Liu: Analyzed and interpreted the data; Wrote the paper. All authors have read and approved to the final version. Zhishun Liu is responsible for the overall content [as guarantor].

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Competing interest

The authors declare no competing interests.

Figure Legend:

Figure 1-Study flowchart

Abbreviations: BPH, Benign Prostatic Hyperplasia

Figure 2-Study Schedule

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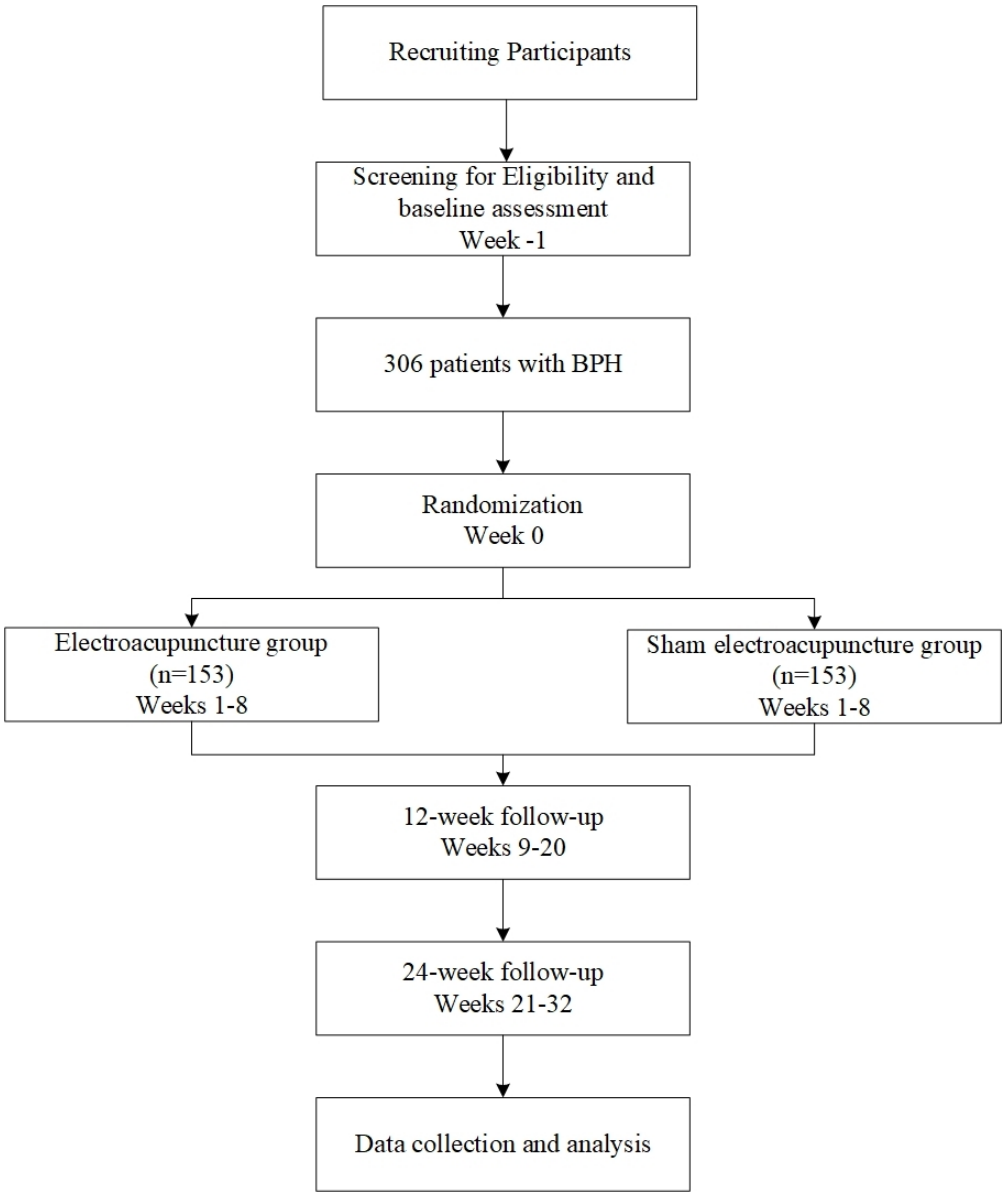

Figure 1-Study flowchart
Abbreviations: BPH, Benign Prostatic Hyperplasia

160x190mm (144 x 144 DPI)

	STUDY PERIOD											
	Enrolment	Allocation	Post-allocation									
			Treatment								Follow-up	
TIMEPOINTS(week)	*-1*	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*12*	*20*	*32*
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Demographics	X												
Medical history	X												
Allocation		X											
INTERVENTIONS:													
Electroacupuncture			←	—	—	—	—	—	—	→			
Sham electroacupuncture			←	—	—	—	—	—	—	→			
ASSESSMENTS:													
International Prostate Symptom Score	X					X				X	X	X	X
Quality of Life	X					X				X	X	X	X
Benign Prostatic Hyperplasia Impact Index	X					X				X	X	X	X
International Index of Erectile Function 5	X									X		X	X
Hospital Anxiety and Depression Scale	X									X		X	X
Hours of Undisturbed Sleep	X					X				X	X	X	X
Volume of prostate	X									X			
Post-void Residual	X									X			
Urinary flow-rate	X									X			
Prostate-specific Antigen	X												
Patient Global Index of Improvement										X		X	X
Expectation assessment	X												
Brief assessment	X									X			
Blinding assessment										X			
Safety assessment	X	X	X	X	X	X	X	X	X	X	X	X	X

Participant Informed Consent

Dear participants:

If your doctor thinks you have benign prostatic hyperplasia (BPH), we invite you to participate in this study aiming to evaluate the efficacy and safety of electroacupuncture (EA) for relieving lower urinary tract symptoms (LUTS) in men with BPH.

Before you decide to participate in the study, please read the following information carefully. It is helpful for you to know this study, understand why the study is performed, the study procedures, the duration and benefits of the study, risks, and potential discomforts during and after study participation.

If you like, you can also discuss this study with your relatives and friends, or consult doctors for explanation and help to make the decision.

I. Introduction

Benign prostatic hyperplasia (BPH) is a common disorder that affect about 36.6% of men aged over 40 years in China. In accordance with the guidelines of the European Association of Urology (EAU) and American Urological Association (AUA), options of the treatment to LUTS in men with BPH range from watchful waiting to medical and surgical interventions, depending on the severity of the symptoms and the level of discomfort, which however may cause side effects. Previous studies suggest that EA may be a potential treatment for BPH.

In this study, a randomized controlled trial design will be used and we aim to evaluate the efficacy and safety of EA for relieving LUTS in men with BPH. This study will be carried out simultaneously in 11 hospitals all over China, and we expect a total number of 306 participants for voluntary participation.

II. Inclusion and exclusion criteria

Participants will be included if they have:

(1) Diagnosis for LUTS attributed to BPH in accordance with the guidelines of EAU and AUA;

(2) Men aged between 40 and 80 years;

(3) LUTS due to BPH for at least 3 months;

(4) International Prostate Symptom Score total score ≥ 8;

(5) Prostate volume ≥ 20 mL;

(6) Maximum urinary flow rate (Qmax)≤ 15 mL/s;

(7) Voluntarily participate in the trial and sign the written informed content.

Participants will be excluded if they have:

(1) Post-void residual urine volume ≥ 150 mL;

(2) Acute urinary retention or catheterization within the 3 months;

(3) Prostate cancer or prostate-specific antigen level (PSA) ≥ 4.0 ng/mL;

(4) Neurogenic lower urinary tract dysfunction; prostatitis; urinary tract infections; urethral strictures; bladder diverticula; bladder stones; bladder cancer; history of genitourinary system surgery (prostate, bladder, urethra, etc.);

(5) Previous acupuncture treatment for BPH in the preceding one month, or usage of α-blockers, 5α-reductase inhibitor, muscarinic receptor antagonists, or any other specific medication in the previous two weeks unless a stable 5α-reductase inhibitor usage of over 3 months;

(6) Severe lung, heart, liver, kidney, metabolic, or mental illness, coagulation dysfunction, or with obvious cognitive dysfunction;

(7) Installed cardiac pacemaker, allergy to metal, severe fear of acupuncture or unbearable to the stimulation of EA.

III. What do you do next, if you decide to participate?

1. Before your enrollment in the study, your medical history will be collected and you will receive a series of examinations to determine whether you are eligible to participate in the study, including physical examination, transabdominal ultrasound, Qmax and PSA. You will also need to complete a series of questionnaires to assess the severity of the disease and the influence on quality of life.

2. If the results of the above screening examinations meet the inclusion criteria and you are willing to participate in this study, you will be invited to continue study participation in the following steps:

(1) Based on the random number generated from the computer, the doctor will assign you to either the traditional acupuncture or minimal acupuncture group. Participants in

the traditional acupuncture group will receive deep needling on the Ciliao (BL32), Zhongliao (BL33), Huiyang (BL35), and Sanyinjiao (SP6) for 30 min; participants in the minimal acupuncture group will receive minimally invasive, superficial needle insertion of 2-3mm on the corresponding acupoints.

(2) In the study, Hwato brand disposable needles (Suzhou Medical Appliance, Jiangsu, China, Jiangsu Food, Drug, and Medical Appliance Administration production approval No.20010020, Registration No:20162200970) will be used.

(3) The duration of this study is 33 weeks in total for a patient including 1-week baseline assessment, 8-week treatment, and 24-week follow up. Frequency and duration of acupuncture: 3 sessions per week in weeks 1-8. The participants will receive 24 sessions of treatment in total.

(4) During the study period, you need to complete the questionnaires faithfully.

3. Other requirements for your cooperation

As a participant of this study, you will have some relevant responsibilities, such as adherence to the schedule for examination, treatment, and clinical follow-up. In addition, you are also responsible for reporting any changes in your physical and mental status to your doctor during the study process regardless of whether you think these changes are related to the study or not. You should follow the scheduled appointments with the doctor to come to the hospital for treatment. Your follow-up is very important because the doctor will determine whether the treatment that you are receiving really works and their safety profile.

During the study, you are not allowed to use other treatments for BPH. However, for intolerable symptoms, medication use such as α-adrenergic blockers is allowed, as long as it is recorded accordingly, including the name and the dosage of the medication use.

IV. Potential benefits of study participation

You may benefit from this study. The benefits may include improvement of symptoms, even by minimal acupuncture. The study may also help doctors and researchers to further evaluate the efficacy and safety of EA for relieving LUTS in men with BPH. The information will be beneficial in the management of other patients with a similar condition in the future. If you decide to participate in the study, you will get relevant

physical and biochemical examination as well the study intervention for free during the study period.

V. Potential side effects, risks, discomforts, and inconveniences

The doctors will make every effort to prevent and treat any side effects brought on by this study. During treatment, you may feel soreness, numbness, heavy, distension sensation, etc., which are normal reactions to acupuncture. EA treatment may have some adverse effects, but it is rare and mild. You may feel fainting due to your individual physique or emotional stress when receive acupuncture needling. Your symptoms should be relieved after the cessation of EA treatment and rest. Localized bleeding, hematoma, and other phenomena may occur after EA treatment, and these phenomena should disappear after applying local pressure. If infection occurs in the needle site, your doctor will handle it timely. With the treatment following the study protocol in the study, if you experience adverse reactions and events related to EA treatment, please feel free to call your doctor for help. The doctor will provide you timely treatment. If injuries have been confirmed and are caused by adverse reactions and events of the study, the study group will deal with them appropriately in accordance with relevant provisions. If you experience any discomfort or new change of your symptoms, or any other unforeseen circumstances during study period, regardless of whether these events are relevant with treatment of the study or not, you shall promptly notify your doctor, and he /she will evaluate the condition and give you appropriate medical treatment.

VI. Payments/compensation for participation

If you participate in the study, during the study, you will get relevant physical and biochemical examination and EA treatment for free. If adverse events occur during the study, they will be managed accordingly by medical experts who will also identify whether they are related to the study or not. The treatment and examination required for your concomitant diseases nonrelated to the study will not be free of charge.

VII. Confidentiality of personal information

All the information related to your participation in this study will be kept confidential by the institute where your participation takes place. Only the institutes responsible for

the study, clinical research institutes, and ethics committees may have access to your medical records. Your name will not appear in any publication or report related to this study. We will make every effort to protect the privacy of your personal medical information as per legal requirements and laws.

VIII. How to acquire extra information?

You can ask any questions about the study at any time and will get answers timely. If we notice any new information that may affect your willingness and decision to continue participating in the study, the doctor will keep you informed.

IX. Can you voluntarily choose to participate in or withdraw from the study?

Whether to participate in this study or not entirely depends on your desire. You can refuse to participate in the study, or withdraw from the study at any time during the study, which will not affect the relationship between you and your doctor and will not affect your medical interests or interests in other areas. For the consideration of your best interests, doctors or researchers may terminate your participation in this study at any time. If you withdraw from the study for any reason, you may be asked for information related of EA treatment or the use of other medications during your participation of the study. If the doctor considers it necessary, you may also be asked to have some laboratory tests and physical examinations performed.

X. What you need to do now?

Decide whether to participate in this study or not. Before you make the decision to participate in the study, please ask your doctor if you have any concerns.

Thank you for reading the above information. If you decide to participate in this study, please tell your doctor, he / she will help you make arrangement for the study.

Please keep this document for your own record.

Informed Consent: Signature Page

Study title: Electroacupuncture for lower urinary tract symptoms in men with benign prostatic hyperplasia: a randomized controlled trial

Organizer of this study: Guang'anmen Hospital, China Academy of Chinese Medical Sciences

Collaborative institute:

Statement of agreement:

I have read the above information about this study and have the opportunity to discuss this study with my doctor and ask questions. All my questions were answered satisfactorily. I understand the potential risks and benefits from participation in this study. I understand the participation of the study is voluntary and I confirm that I was given sufficient time for consideration of study participation. I confirm that I understand that:

I can always ask the doctor for additional/more information.

I can withdraw from the study at any time without discrimination or retaliation and my medical treatment and interests will not be affected.

I understand that if I withdraw from the study, I will tell the doctor the changes of my disease condition and complete the relevant physical and biochemical examinations if needed, which will be very helpful for the whole study.

If I need to take any other medications due to the changes of my medical condition, I will seek medical advice from the doctor beforehand or afterwards tell the doctor truthfully.

I agree to allow the research institute, collaborative institutes, and ethics committees to inspect the data relevant to my study participation.

I will receive a signed and dated copy of the informed consent form.

Finally, I decide and agree to participate in this study and ensure the adherence to doctor's orders to the best I can.

Signature of patient: Year month day

Telephone:

I confirm that I have explained this study in detail to the patient, including patient's rights as well as the potential benefits and risks, and have given the patient a signed copy of the informed consent form.

Signature of doctor: Year month day

Office phone number of doctor:

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: Page 2-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry: Page 2
	2b	All items from the World Health Organization Trial Registration Data Set: NA
Protocol version	3	Date and version identifier: NA
Funding	4	Sources and types of financial, material, and other support: Page 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors: Page 1,19
	5b	Name and contact information for the trial sponsor: NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee): Page 14-15
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: Page 4-5
	6b	Explanation for choice of comparators: Page 4-5
Objectives	7	Specific objectives or hypotheses: Page 5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory): Page 5-6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained: Page 5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists): Page 7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: Page 8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease): NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests): NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial: Page 10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended: Page 10-14, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure): Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations: Page 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size: Page 6-7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions: Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned: Page 8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions: Page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how: Page 8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial: NA
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol: Page 14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: Page 14-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol: Page 14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol: Page 15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses): Page 15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation): Page 15-16

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed: NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial: NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct: Page 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor: NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: Page 16-17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators): NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32): Page 16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial: Page 16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site: Page 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators: NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation: NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions: NA
	31b	Authorship eligibility guidelines and any intended use of professional writers: NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code: NA
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates: Supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable: NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.